European Crohn's and Colitis Organisation Topical Review on Complementary Medicine and Psychotherapy in Inflammatory Bowel Disease

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Abstract: Patients with inflammatory bowel disease [IBD] increasingly use alternative and complementary therapies, for which appropriate evidence is often lacking. It is estimated that up to half of all patients with IBD use various forms of complementary and alternative medicine during some point in their disease course. Considering the frequent use of such therapies, it is crucial that physicians and patients are informed about their efficacy and safety in order to provide guidance and evidence-based advice. Additionally, increasing evidence suggests that some psychotherapies and mind-body interventions may be beneficial in the management of IBD, but their best use remains a matter of research. Herein, we provide a comprehensive review of some of the most commonly used complementary, alternative and psychotherapy interventions in IBD.

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European Crohn's and Colitis Organisation Topical Review on Complementary Medicine and Psychotherapy in Inflammatory Bowel Disease

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1. ABSTRACT

Patients with Inflammatory Bowel Disease increasingly use alternative and complementary therapies, for which appropriate evidence is often lacking. It is estimated that up to half of all patients with IBD use various forms of complementary and alternative medicine during some point in their disease course. Considering the frequent use of such therapies, it is crucial that physicians and patients are informed about their efficacy and safety in order to provide guidance and evidence-based advice. Additionally, increasing evidence suggests that some psychotherapies and mind-body interventions may be beneficial in the management of IBD, but their best use remains a matter of research. Herein, we provide a comprehensive review of some of the most commonly used complementary, alternative, and psychotherapy interventions in IBD.

2. INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disease where both medical and psychological factors have a major impact on patient´s quality of life (QoL). Many patients seek alternative and complementary therapies,[1] for which appropriate evidence is often absent. However, considering the increasing use of such therapies, it is important that physicians are ready to provide evidence-based advice on their efficacy and potential risks.

High levels of psychological and emotional distress, fatigue, anxiety, and depression are common among IBD patients, all complex symptoms that require integrative and appropriate management[2,3]. Psychotherapies and mind-body interventions may have beneficial impact on coping skills and stress management, but their best use remains undetermined.

The aim of this topical review is to provide an overview on the most commonly used complementary, alternative, and psychotherapy interventions used in IBD.

3. METHODS

The European Crohn's and Colitis Organisation (ECCO) organized a topical review consensus group on the issue of Complementary Medicine and Psychotherapy in IBD. ECCO topical reviews are developed from expert opinion consensus and are endorsed by ECCO. As controlled data are absent, a topical review is distinct from ECCO consensus guidelines and is intended to provide guidance in clinical areas where scientific evidence is lacking. An open call was announced to all ECCO members; 15 individuals were selected based on their expertise in the topic. Three subgroups were formed. Working Group 1 focused on biologically-based practices with the goal of reviewing products such as herbal medicines, probiotics, marijuana, vitamins, and other dietary supplements. Working Group 2 focused on mind-body practices and psychotherapy interventions, with the goal of reviewing the main psychological domains that are altered in IBD (anxiety, depression, fatigue, etc). The available evidence for the use of hypnosis, yoga, and psychotherapy interventions was reviewed. Finally, Working Group 3 focused on manipulative and body-based practices such as acupuncture and exercise.

All working groups performed a systematic literature search of their topic. Discussions of the published evidence among the working group members and a preliminary voting round took place. The working parties met in Vienna in February 2018 to agree on the statements. Statements were accepted when 80% or more of the participants were in agreement; statements were henceforth termed an agreed *Current Practice Position.* The group leaders and their respective working group wrote the final section for each subgroup. It is intended that the statements are read in context, with qualifying comments and not in isolation. The final text was edited for consistency of style by the steering committee and one member of the Guidelines Committee of ECCO who were not involved in the consensus. We recognize that not all products or interventions have

been included in this review as we chose to focus only on those that are most widely used.

4. HERBAL THERAPIES AND DIETARY SUPPLEMENTS

Many studies have assessed a wide range of herbal therapies and different herbal preparations in IBD. These are summarized in Table 1.

a. *Cannabis* and other herbal therapies

Current Practice Position 3.1
Although the use of *Cannabis* may be associated with a reduction of some symptoms in IBD, there is no good evidence to show that it positively affects the course of disease

A retrospective observational study on 30 patients showed promising results for *Cannabis* for the treatment of active Crohn's disease (CD).[4] A RCT assessed 22 patients who received either *Cannabis sativa* or placebo cigarettes.[5] Response rates and QoL, but not remission rate or reduction of C-reactive protein (CRP), were higher in the intervention group.[5] Side effects did not differ between the groups.

Two small controlled studies reported on the use of *Artemisia absinthium* (wormwood), a herbaceous plant, compared to placebo[6] or standard treatment[7] for the treatment of active CD (Table 1).

Current Practice Position 3.2

Curcumin as a complementary therapy to 5-aminosalicylic acid (5-ASA) may be effective in inducing remission in mild-to-moderately active ulcerative colitis (UC). Curcumin, psyllium, and an herbal preparation consisting of myrrh, chamomile, and coffee charcoal may be effective as complementary maintenance therapy in UC.

For maintenance of remission in CD**,** a *Boswellia* extract compared to placebo was investigated in a RCT of 82 patients. There were no significant differences between the groups after 12 months. There were no serious adverse events in both groups.[8] Another study tested the effects of a traditional Japanese herbal preparation (*daikenchuto*) compared to 5-ASA and azathioprine among patients who underwent surgery. The results of this study indicated a significantly lower 3-year reoperation rate in the *daikenchuto* group.[9]

High doses of *Tripterygium wilfordii* Hook F, a plant widely used in Chinese traditional medicine, led to prolonged remission and was well tolerated.[10-13] For prevention of postoperative recurrence, *Tripterygium wilfordii* was less effective than azathioprine in the long-term.[10-13]

For treatment of active UC, no differences regarding disease activity or remission rates were observed with curcumin enema plus oral mesalamine, as compared to placebo enema plus oral mesalamine.[14] Oral curcumin plus oral mesalamine compared to placebo plus oral mesalamine resulted in more patients achieving endoscopic remission at the end of the 1-month treatment period and more patients with clinical improvement in the curcumin group.[15] The incidence of adverse effects was not different between the treatments.

A study on 44 patients compared *Aloe vera* gel to placebo and showed significant improvements in clinical signs and QoL after 4 weeks. Reductions in histologic score were also observed. No serious adverse events were reported.[16]

Two studies evaluated the effects of HMPL-004 (*Andrographis paniculata*).[17,18] No significant differences were found in one study, while in the other study higher response rates were observed with HMPL-004. The effects of pomegranate (*Punica granatum*) peels plus standard treatment were compared to placebo plus standard treatment in a study on 79 patients.[19] Clinical treatment response was higher in the *Punica granatum* group, although this was not statistically significant.

Wheat grass showed positive effects on disease activity, rectal bleeding, and abdominal pain.[20] Another study on 126 patients assessed *Sophora* colon-soluble capsules or mesalamine over a period of 8 weeks[21]. There were no significant differences between groups regarding disease activity or laboratory measurements.

For maintenance of remission in UC**,** curcumin had positive effects on disease activity and recurrence rate at 6 months.[22] Curcumin is only available as an over-the-counter food supplement and relevant quality concerns regarding the preparation of the herbs may be an issue.

Treatment with an herbal preparation of myrrh, chamomile, and coffee charcoal versus mesalazine exhibited no significant differences between the treatment groups regarding relapse rates, relapse-free time, endoscopy, and faecal biomarkers.[23] The herbal preparation was well tolerated and had a good safety profile. This preparation is available as a drug at least in single countries in Europe.

A study on 80 patients revealed that silymarin in addition to standard therapy had positive effects on haemoglobin levels, erythrocyte sedimentation rate, and disease activity.[24] However, no significant differences between groups were reported.

Preliminary evidence indicates that *Holarrhena antidysenterica* might be effective but study quality was very low.[25]

Traditional Chinese Medicine (TCM*)* herbs are individualized based on symptoms and treatments are often based on classification of disease patterns. Accordingly, a conclusion about TCM herbs cannot be provided. However, TCM shows promising evidence.[26-29]

Other herbs not yet evaluated by RCTs show promise in treating IBD. An open pilot study explored the effects of an anthocyanin-rich bilberry preparation in 13 patients with active UC. Over half (63.4%) of the patients achieved remission and 90.9% showed a response.[30]

An open-label, dose-escalating study on 16 patients with active UC assessed tormentil in escalating doses for 3 weeks. During tormentil treatment, Colitis Activity Index decreased with highest effect sizes for 1800, 2400, and 3000 mg/day.[31]

A non-randomized observational clinical study assessed an ayurvedic preparation (extract of *Holarrhena antidysenterica*, decoction of *Ficus glomerata*, powder combination of *Cyperus rotundus*, *Mesua ferrea*, and *Symplocos racemose* and *Ficus glomerata* decoction) in UC patients. Reductions in bowel movements, blood in the stool, and abdominal pain and improvements in general well-being and reduced intake of aminosalicylates were observed.[32]

In summary, only few and small trials have investigated the role of herbs in the therapy of IBD patients with limited quality, which probably limits their routine use in the clinic.

b. Vitamins and minerals

Current Practice Position 3.3
There is insufficient evidence to support the use of vitamins and minerals to induce or maintain remission in CD and UC

Therapy with vitamin D,[14,33-56] vitamin B,[57-59] and vitamin K[60] has been examined regarding their possible involvement in inflammatory pathways in IBD.

Vitamin D deficiency is multifactorial in IBD and ranges between 10% to 75% across studies.[61] The causes of vitamin D deficiency in patients with IBD include inadequate exposure to sunlight from reduced physical activity, inadequate dietary intake, impaired absorption, and impaired conversion of vitamin D.[61]The use of vitamin D as a therapy has been explored in vitamin D-deficient IL-10 knockout mice, which develop a rapidly progressive form of IBD. Disease was attenuated when these mice were given a high calcium and vitamin D diet.[62] Some human studies have examined the role of vitamin D in IBD treatment.[35,36,40,63] A study on use of vitamin D as maintenance therapy in CD patients in remission demonstrated that only 13% of the patients in the vitamin D replacement group relapsed during the 12-month study period compared to

29% in the placebo arm (p = 0.06).[36] Another group compared the therapeutic effects of vitamin D replacement on bone health and CD activity and reported significant improvement during the 6-week follow-up period.[35] An accelerated supplementation protocol for patients with CD or UC led to significant improvement in symptom-based activity scores (CDAI) but not in objective markers of inflammation.[55]

A recent meta-analysis revealed that vitamin B12 levels were significantly lower in IBD patients than in healthy controls (standardized mean difference [SMD] -0.57 pg/mL; p < 0.001). However, there was significant heterogeneity in the included studies.[59] Mortimore and Florin reported the impact of high-dose vitamin B12 on the treatment of 10 consecutive IBD patients with dermatoses and showed improvement in cutaneous manifestations in 6 patients but not in those with only fistulising CD.[58]

A recent review reported the prevalence of vitamin K deficiency in 111 paediatric IBD patients as 54% (CD) and 43.7% (UC), which correlated with higher disease activity and was most likely due to malabsorption and malnutrition.[64] In a study from the Framingham Offspring population, vitamin K levels were inversely correlated with inflammatory markers (such as CRP); it was postulated that vitamin K may have anti-inflammatory properties.[65] One study reported no significant effects of vitamin K supplementation on bone health status in patients with CD.[60] No study has investigated the effects of vitamin K supplementation on disease activity in IBD.

c. Dietary supplements

Current Practice Position 3.4

There is insufficient evidence to support the use of diet supplements or specific diets to induce or maintain remission in CD and UC. However, future research should focus on diet as a complementary therapy

This section is focused on dietary supplements other than enteral or parenteral nutrition. A more comprehensive review on diet and nutrition has been published in a separate Topical Review.[66]

Common nutritional and dietary supplements comprise dietary fibre supplements (including prebiotics such as fructo-oligosaccharides) and fatty acids. The theorized mechanism underpinning the pathogenesis of IBD is an aberrant response by the mucosal immune system to microbiota in genetically susceptible individuals.[67] Short-chain fatty acids such as butyrate, arising from anaerobic fermentation of dietary fibre, are thought to positively influence the gut microbial composition and enhance colonic epithelial barrier function.[68-80] The tested forms of fibre delivery in IBD range from dietary advice[81] to fibre supplementation. Such supplementation includes psyllium[67,81,82] and germinated barley.[83-85] A systematic review of three RCTs in UC and one study in pouchitis revealed positive results for the use of fibre supplementation.[67] No studies in CD showed added benefit [86-88], while others showed

equivalence [89,90]. The trials examined showed conflicting results. Treatment of UC patients with germinated barley revealed a significant reduction in CRP but not in clinical activity indices.[83] However, a separate study on UC patients revealed a significant reduction in clinical indices, but not CRP, after administration of germinated barley.[85]

Fructo-oligosaccharides are prebiotics that are non-digestible, selectively fermentable, short-chain carbohydrates that stimulate the growth or activity of selected beneficial microbial species, such as *Faecalibacterium prausnitzii* and Bifidobacteria, resulting in potential health benefits to the host.[88] An open-label pilot study on CD patients revealed a significant reduction in Harvey-Bradshaw index (HBI) and a non-significant reduction in inflammatory markers (CRP).[91] This study was followed up with an adequately powered RCT that did not show a statistically significant different clinical response.[88] Another RCT showed a significant reduction in HBI compared with baseline.[92]

Specific diets, such as a diet high in salmon,[93] have been examined for the treatment of IBD. The purported benefit of salmon is its high *n*-3 polyunsaturated fatty acid (PUFA) content (omega-3), with the additional benefit of peptides and phospholipids that accompany the fish (see also next paragraph).[93] *n*-3 PUFAs are thought to produce an anti-inflammatory effect through the reduction of pro-inflammatory cytokines.[93] A single-arm open-label pilot study on 12 patients that assessed the efficacy of a salmon-rich diet in patients with mild-to-moderate UC revealed that an intake of 600 g of salmon weekly over 12 weeks significantly reduced disease activity ($p < 0.01$), was associated with a trend towards lower CRP, and increased the anti-inflammatory fatty acid index in biopsies and plasma.[93]

Despite the current deficiency of quality data for diet supplements or specific diets in IBD, dietary therapies have the potential to be a meaningful complementary treatment and should be the focus of future research.

d. Fish oil – omega-3 fatty acids

Current Practice Position 3.5

Omega-3 fatty acids might be beneficial in maintaining remission in CD. However, study quality and heterogeneity of trials limit these findings

Fish oil, or *n-3* PUFA, is thought to reduce production of IL-1, IL-6, and tumour necrosis factor.[94] Oxidative stress, caused by an imbalance between the formation of reactive oxygen species and counteracting antioxidants occurs in several chronic inflammatory conditions, including IBD. Increasing the antioxidant level might reduce tissue damage and the inflammatory process. Fish and fish proteins may have such an antioxidant potential.[95-97] A beneficial effect of fish oil and fish protein has been shown in some

animal models.[95] Fish oil is found predominately in oily fish and in commercially produced fish oil capsules. Several studies have been conducted to test the effect of omega-3 fatty acid (FA) supplementation (also called *n*-3 or ω-3 FA) on biochemical and clinical outcomes in IBD.

Among CD patients, two studies[98,99] assessed the effect of *n*-3 FA compared with *n*-6 FA on biochemical and clinical markers of inflammation as adjuvant therapy to corticosteroid treatment in patients with active disease. Nielsen et al (*N* = 31) showed that *n*-3 FA had immunomodulatory properties and might inhibit the increase of proinflammatory cytokines in contrast to *n*-6 FA. Eivindson et al (*N* = 31) showed that disease activity and CRP decreased from baseline to week 9 in both the *n*-3 and the *n*-6 group.[99]

A Cochrane review[94] that assessed *n*-3 FA for the maintenance of remission in CD found a marginal benefit for *n*-3 FA over placebo in preventing relapse after one year (relapse rate, *n*-3 group 39% versus placebo 47%, 6 studies, 1039 patients, relative risk [RR] 0.77, 95% confidence interval [CI] 0.61–0.98). The same trend was also found in two other systematic reviews.[100,101] Patients with CD had a significant reduction of relapse risk within one year compared with placebo in favour of *n*-3. However, there was heterogeneity in the pooled analyses, publication bias, and small negative trials were underestimated. In addition, no reduction in 1-year relapse rate was observed in the two high-quality studies EPIC1 and EPIC2.[102]

In patients with UC, two systematic reviews found no difference in the relapse rate between *n*-3 FA supplementation and control groups.[100,103] These studies did not record significant adverse events.

A RCT on 211 patients assessed the effect of a combination of a nutritionally balanced oral supplement enriched with fish oil, fructo-oligosaccharides, gum arabic, vitamin E, vitamin C, and selenium on disease activity and medication use in adults with mild-to-moderate UC. This study revealed similar rates of improvement of disease activity score and need for corticosteroids over a 6-month period as placebo[104]. Studies assessing the effect of fish oil on extraintestinal manifestations (such as joint pain) via administration of seal oil have shown promising results.[105-107] A study that compared seal oil and cod liver oil found a tendency toward improvement in several joint pain parameters for both oils.[107] Another study found positive results for duodenal administration of seal oil (rich in *n*-3 FAs) compared with soy oil (rich in *n*-6 FAs). Soy oil tended to aggravate joint pain.[105]

e. Probiotics

Current Practice Position 3.6

There is no evidence to support the use of prebiotics, probiotics, or both in patients with CD, neither in the induction nor maintenance of remission. There is no evidence to support the use of prebiotics, probiotics, or both in the postoperative CD patient.

A recent overview summarized the evidence for probiotics in IBD patients.[108] Two trials (*N* = 37) evaluated the efficacy of probiotics in the induction of remission in CD.[109,110] Both studies failed to show a clinical benefit. Studies evaluating maintenance of remission in quiescent CD patients (*N* = 195) also failed to show a statistically significant benefit.[111,112] The role of probiotics in preventing relapse in CD patients in remission following surgically-induced remission (*N* = 333) remains controversial and no recommendations on their use can currently be given.[113-116] In summary, there is little evidence for the use of probiotics in the treatment of CD.

Current Practice Position 3.7

Escherichia coli Nissle 1917 may be effective in inducing and is effective in maintaining remission in UC. A multistrain probiotic containing a combination of lactic acid bacteria, streptococcus, and bifidobacteria may be effective in inducing and maintaining remission in UC.

Eight studies evaluated the efficacy of probiotics in inducing remission in patients with active UC.[117-124] One study compared nonpathogenic *Escherichia coli* Nissle 1917 b.d. for 12 weeks with mesalazine for 12 weeks (*N* = 116).[121] There was no statistically significant difference between the two groups. The other seven studies (*N* = 535) were RCTs that compared probiotics with placebo.[117-120,122-124] Three of these trials (*N* = 319) used a multistrain probiotic containing eight different probiotics (*Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*).[119,122,124] A recent systematic review[108] calculated on those three studies showed a number needed to treat of 5 for this multistrain probiotic (95% CI 4–10). Six RCTs evaluated the efficacy of probiotics (*Bifidobacterium longum*, *Lactobacillus acidophilus*, *Bifidobacterium animalis* subsp. lactis BB-12, *Escherichia coli* Nissle 1917, *Streptococcus faecalis* T-110, *Clostridium butyricum* TO-A, and *Bacillus mesentericus*) in the maintenance of remission in quiescent UC.[125-130] Of these trials, three compared probiotics with 5-ASAs (*N* = 555)[126,127,130] and three compared probiotics with placebo (*N* = 122).[125,128,129] In summary, probiotics showed efficacy in maintaining remission in UC patients. Since probiotics are usually well tolerated, they are useful alternatives to conventional medical therapy especially in UC patients.

5. MIND-BODY MEDICINE AND PSYCHOTHERAPEUTIC INTERVENTIONS

A significant proportion of IBD patients report or suffer from depression, anxiety, or both. The prevalence rates of these disorders have been evaluated in four systematic reviews[131-134] and two large observational studies,[135,136] where they were compared between IBD and healthy and medically ill controls.

a. Anxiety

Current Practice Position 4.1

There are data showing higher rates of anxiety preceding the diagnosis of IBD in adult patients

Current Practice Position 4.2

Anxiety is common in IBD, particularly during flares, with higher rates than in healthy controls but not in medically ill controls. Anxiety is slightly more common in CD than UC

Adults with IBD are more likely to develop anxiety before IBD onset; 70% of those with IBD and a lifetime history of anxiety or a mood disorder had a first episode of an anxiety disorder 10 years or more before the IBD diagnosis, whereas just 8% developed anxiety ≥2 years after IBD onset.[136]

The pooled prevalence estimate for anxiety disorders in adult IBD patients is 20.5% (95% CI 4.9–36.5%).[133] In CD, the pooled rate of anxiety-related symptoms is 19.1% (±3.63, 95% CI), 28.2% (±2.7, 95% CI) during remission, and 66.4% (±7.8, 95% CI) during flares (37% [±9.9, 95% CI]) [132]. In UC the pooled rate of anxiety symptoms is 31% (±14.2, 95% CI) as compared to 9.6% (±1.94, 95% CI) in healthy controls.[132]

In studies where IBD cases were compared with medically ill controls, the pooled average rate of anxiety symptoms was 41.9% (±9.2, 95% CI) for IBD and 48.2% (±31.1, 95% CI) for medically ill controls.

b. Depression

Current Practice Position 4.3

There is data showing higher rates of depression preceding IBD diagnosis in adult patients

Current Practice Position 4.4

Depression is common in IBD, particularly during flares, with higher rates than in healthy controls but not in patients with other chronic diseases

Similar to anxiety, 54% of adult IBD patients with a lifetime history of anxiety or mood disorders had an onset of depression ≥2 years before IBD onset while 23% developed depression ≥2 years after IBD onset.[136]

The pooled prevalence of depressive disorders in adults is 15.2% (95% CI 9.9–20.5%). The pooled mean rate of depressive symptoms in IBD is 21.2% (±2.9, 95% CI) compared with 13.4% (±1.9, 95% CI) for healthy controls,[132] with a higher prevalence in CD (25.3%, 95% CI 20.7–30%) than UC (16.7%, 95% CI 12.0–21.4%) and higher in active (40.7%, 95% CI 31.1–50.3%) versus inactive disease (16.5%, 95% CI 7.4–25.5%).[133] In the studies with medically ill controls, the pooled mean depression rate was 14.5% (±10.5, 95% CI) in IBD versus 28.4% (±17.7, 95% CI) in medically ill controls.

c. Stress

Patients often report stress as a major trigger of both disease and flares; this association has been examined in several studies.[3,137-142] In a population-based study (*N* = 704), only high-perceived stress was associated with an increased risk of flare (adjusted odds ratio [OR] 2.40, 95% CI 1.35–4.26).[140] In two prospective studies[3,142] each approximately with almost 500 participants, perceived stress was associated with symptomatic activity for both CD and UC. Patients with persistently active disease reported significantly higher stress than the persistently inactive group (mean stress at 3-month follow up 23.64, 95% CI 21.81–25.46 versus 17.46, 95% CI 16.46–18.45).[142] A smaller prospective study on CD patients (*N* = 101) also found stress, when paired with avoidance coping, as a significant predictor of flare.[141]

Current Practice Position 4.5

There is some evidence that stress is associated with a higher risk of relapse in IBD. There is no data on stress contributing to the aetiology of IBD

d. Fatigue

Current Practice Position 4.6

Even if inconsistently defined in the literature, fatigue is common in IBD patients and affects social functioning and QoL. Fatigue is associated with anxiety or depression, disease activity, sleep disturbances, reduced physical activity, medication use, and anaemia

Despite extensively studied,[2,143-160] fatigue has been inconsistently defined in the literature and commonly reported as a secondary outcome.[144] Vogelaar et al found that several immune parameters were higher in fatigued patients, including TNF-α (p = 0.02) and IL-12 (p < 0.001); IL-6 was lower in these patients (p = 0.002).[156]

The reported fatigue prevalence in IBD ranges between 22% to 48% in remission and 44% to 86% in moderate-to-severe active disease.[2,143,149] Almost 50% of newly diagnosed patients report fatigue.[150] Severe anaemia can cause fatigue,[146,147] but this is not the case with iron deficiency without anaemia.[152] Other contributors include nutritional deficiency, smoking, and immune and genetic factors.[145,146,148,156] In an observational study of 631 patients, 50% of patients with anaemia experienced daily fatigue, irrespective of disease activity.[153] In a cross-sectional survey (N = 5382), prolonged use of corticosteroids was associated with fatigue versus non-use (55% versus 51%; p = 0.001) in patients aged >60 years.[154] In a systematic review,[148] depression, stress, sleep disturbances, and anxiety (in this order) were associated with IBD fatigue. Fatigued patients reduce physical activity, with an estimated effect size of 1.02 (p = 0.04).[155] Exercise programs could address the physical component of IBD fatigue.[155,158] Fatigue reduced QoL in three studies (N = 84).[147] Low QoL can in turn increase fatigue.[151]

e. Irritable bowel syndrome (IBS) and functional symptoms in IBD

The evidence on functional GI disorders is mostly limited to irritable bowel syndrome (IBS)-type symptoms.[161-166] The pooled prevalence of IBS in IBD is approximately 39% (95% CI 30–48%),[166] and is slightly lower during remission (35%, 95% CI 25–46%) than during flares (44%, 95% CI 24–64%). When compared with controls, the OR for IBS was 4.89 (95% CI 3.43–6.98) in all IBD patients, 4.39 (95% CI 2.24–8.61) in remission, and 3.89 (95% CI 2.71–5.59) in active disease. The prevalence of IBS in CD was higher than in UC (46% versus 36%; OR 1.62, 95% CI 1.21–2.18). In a recent cross-sectional study (N = 6309), Abdalla et al[161] observed a 20% rate of self-reported IBS diagnosis. Two large studies (N = 1321 with IBS-like symptoms, N = 6401 for all IBD patients) revealed worse QoL, higher levels of anxiety, depression, fatigue, sleep disturbances, pain interference, and decreased social satisfaction in patients with IBS-like symptoms.[161,165]

A cross-sectional study on children (N = 184)[162] found that the prevalence of IBS-type symptoms was highly dependent on the definition of remission.

Current Practice Position 4.7

IBS is common in IBD and is associated with adverse patient-reported outcomes. IBS is slightly more common in CD than in UC

f. Sleep

Evidence regarding sleep disturbance in IBD is based on two case-control studies,[167,168] five cohort studies,[169-172] and one cross-sectional study.[173]

The prevalence of sleep disorders in IBD ranges between 44% and 66% (versus 27–55% in healthy controls and 67–73% in IBS).[168,169,171,173] Even in remission, IBD patients (*N* = 119) report significantly more sleep disturbance (prolonged sleep latency, frequent sleep fragmentation, high use of sleeping pills, and poor overall sleep quality) than healthy controls; rates were however similar to IBS.[167] Sleep disturbance is slightly more common in CD than in UC.[167] Two prospective cohort studies[171,172] (*N* = 3214) found an association between poor sleep quality and disease activity. Several cohort studies (*N* = 1468) suggest an association between poor sleep quality and an increased risk of IBD relapse at 6 months to 1 year.[169,171,174]

Current Practice Position 4.8

There is limited evidence on the frequency of sleep disturbance in IBD. Some studies report higher rates of sleep disturbance in IBD than in healthy controls

In summary, anxiety and depression are common in IBD. High perceived stress is associated with a higher risk of relapse. Fatigue is common in IBD and is associated with higher disease activity and increased rates of anxiety and depression. IBS is common in IBD and is associated with poorer patient-reported outcomes. There is limited evidence on the frequency of sleep disturbance in IBD and further studies focused on sleep in IBD are needed.

g. Cognitive Behavioural Therapy (CBT)

Current Practice Position 4.9

Cognitive behavioural therapy (CBT) has a short-term beneficial effect on QoL in adults with IBD. There is limited evidence on the efficacy of CBT in adolescents; early reports are promising in terms of QoL and coping

CBT is a type of psychotherapy that teaches patients to identify and modify unhelpful negative thinking styles and maladaptive behaviours. It has a shorter duration than traditional psychotherapies (6–12 weeks).[139] Common elements of CBT include exploration of the links between cognitions and emotions, cognitive restructuring and challenging unhelpful thoughts, psycho-education, coping, and relaxation.

The evidence on the effectiveness of CBT in IBD has been summarized in two meta-analyses[138,175] and two systematic reviews.[139,176] CBT seems to improve the short-term QoL in adults (*N* = 254, SMD 0.37, 95% CI 0.02–0.72),[175] albeit with little or no effect on disease activity, anxiety, depression, and perceived stress.[139,176] A positive short-term effect of CBT on QoL (SMD 0.70, 95% CI 0.21–1.18) and coping (SMD 0.75, 95% CI 0.26–1.25) was noted in adolescents (*N* = 71).[138]

h. Hypnotherapy

Current Practice Position 4.10

There is limited evidence on the efficacy of hypnotherapy to reduce IBD symptoms, maintain clinical remission, and increase QoL in UC

The effectiveness of hypnotherapy (treatment involving deep relaxation, focused attention, and an enhanced ability to follow suggestions) has been studied in IBD.[138,139,175,177] A small study showed an immune-modulating effect of a 50-minute session of gut-directed hypnotherapy in 17 patients with active UC.[139,177] Three pre-post hypnotherapy studies (*N* = 2, CD, with a 6-month follow up; *N* = 8, IBD; *N* = 15, severe UC with 5.4-year follow up) and one trial in UC (*N* = 23) have shown that hypnotherapy improves QoL and reduces bowel symptoms.[139,177] One RCT in quiescent UC (*N* = 54) showed that gut-directed hypnotherapy maintains clinical remission (68% for hypnosis versus 40% of controls maintained remission for 1 year; $p = 0.04$).[139,175,177]

i. Other psychotherapies

Current Practice Position 4.11

Psychodynamic therapy may reduce depressive and anxiety symptoms. Stress management has only modest benefits in reducing IBD symptoms and improving mental health or QoL. Solution-focused therapy (SFT) might be beneficial for patients with fatigue

The evidence on the effectiveness of psychodynamic therapy and as well as SFT in IBD is based on two meta-analyses and two systematic reviews[138,139,175,176]. Other psychotherapies such as psychodynamic (PD) therapy and stress management (SM) interventions have also been investigated in IBD.[138,139,175,176] PD is derived from traditional psychoanalysis and focused on working with transference (i.e., the redirection of childhood emotions to a therapist). Common elements of PD are interpretation, empathic validation, free association, and analysis of transference, regression, and resistance.[139] PD must be used as a long-term therapy (20–52 weeks in IBD trials). SM is focused on developing strategies to manage stress and includes breathing exercises, relaxation, biofeedback, and problem solving (typically 6–8 sessions). SFT uses the patient's past experiences to address current difficulties and relies on identifying solutions that worked in the past and finding exceptions to the patient's problems (typically 5–6 sessions). No or minimal effect of PD, SM, and SFT on long-term disease activity have thus far been observed.[138,139,175,176] Significant short-term improvements in QoL and fatigue were observed in patients with elevated fatigue scores receiving SFT.[175] There is limited evidence for SM and PD to improve mental health and QoL.[139,176]

j. Meditation, mindfulness, and relaxation

Current Practice Position 4.12

Meditation and relaxation may improve QoL and possibly decrease inflammatory activity in IBD. There is limited evidence on the effectiveness of mindfulness-based interventions on disease activity

Meditation is a broad term encompassing practices aimed at reaching a heightened level of consciousness and concentration. Mindfulness is a type of meditation dedicated to being present in the moment. It involves activities where one focuses on a particular sensation, such as taste or smell, and brings the mind to breathing. Relaxation is a process of reducing tension in the body and mind and may involve breathing activities or tensing and relaxing different muscle groups. Meditation, mindfulness, and relaxation are often used as part of psychotherapies but also as standalone treatments to promote wellbeing.

While older trials in IBD ($N = 136$) reported improvements in symptoms, psychosocial wellbeing, and QoL using relaxation and stress management, recent trials found benefit on QoL only (2 RCTs, $N = 121$).[178] Two recent studies ($N = 29$[179] and $N = 60$[180]) showed that mindfulness improved psychological and physical symptoms in IBD and reduced CRP levels.[179] Norton et al[181] showed pain reduction using relaxation, meditation, or both in four out of six studies. Timmer et al[138] showed no evidence for the efficacy of relaxation in unselected adults with IBD.

h. Yoga

Current Practice Position 4.13

There is limited evidence on the efficacy of yoga to reduce IBD symptoms. Yoga improves QoL in adults with IBD

The largest survey performed to date (N = 235)[182] reported that 16.3% of paediatric IBD patients (aged 2–22 years) practiced yoga, meditation, or tai chi, while the second survey (N = 67, aged 12–19 years) reported that 10% of patients practiced yoga.[183] One trial[184] (N = 60, UC; N = 40, CD; all adults in remission) compared an 8-week yoga intervention to treatment as usual (TAU). The study showed yoga to be no different than TAU, except for colic pain that was reduced in the yoga group ($p < 0.05$). Another RCT[185] (N = 77; adults with UC in remission) on patients with impaired QoL who received 12 sessions of yoga or written self-care advice showed yoga to be effective in improving QoL after 12 and 24 weeks (p = 0.018 and p = 0.022, respectively). Yoga also improved disease activity after 24 weeks (p = 0.029).

In summary, CBT improves QoL in IBD over the short term. Although the evidence on the efficacy of hypnotherapy to reduce IBD symptoms is limited, the efficacy of hypnotherapy in functional gut disorders[186] warrant future studies in IBD. PD therapy and SM may reduce depressive and anxiety symptoms, but not IBD severity. SFT might be beneficial for patients with fatigue. Meditation and relaxation may improve QoL and inflammatory activity in IBD. Evidence on the effect of mindfulness-based interventions on disease activity is limited and the role of this intervention in IBD management should be further explored. There is limited evidence on the efficacy of yoga to reduce IBD symptoms, but yoga may improve QoL in adults with IBD.

6. MANIPULATIVE AND BODY-BASED INTERVENTIONS

a. Moxibustion and acupuncture

Current Practice Position 5.1

There is insufficient evidence to support the use of moxibustion and acupuncture (either in monotherapy or in combination) for the treatment of active UC or CD

The term acupuncture (AP) refers to the insertion of needles for remedial purposes into specific points (acupoint receptors).[187] Moxibustion is a procedure involving the use of heat generated by burning material, which is then applied to certain areas of the body (usually AP points[187]) where it stimulates superficial and deep tissues of the skin.[188] Several burning materials can be used, the most usual being moxa (herbal preparation containing *Artemisia vulgaris)*. Direct moxibustion is applied directly to the skin around an acupuncture point, whereas indirect moxibustion or herb-partitioned

moxibustion (HPM) is performed with some insulating materials between the moxa cone and the skin.[187-189] AP and moxa are often used in combination. [187] Several human studies have assessed the clinical benefit of these interventions in IBD (Supplementary Table 1).

Moxibustion alone

A systematic review and meta-analysis assessed the evidence of moxibustion alone for the treatment of UC;[189] five RCTs conducted in China were included, three of which compared moxibustion with sulfasalazine (SASP) and the remaining two compared moxibustion to SASP and other drugs (antibiotics, steroids). The efficacy of moxibustion was based on physician's assessment (recovery, marked improvement, improvement, and no change) or endoscopy. The meta-analysis suggested a small favourable effect of moxibustion when compared with SASP alone (RR 1.23, 95% CI 1.04–1.46; $p = 0.01$) or SASP combined with steroids or antibiotics (RR 1.33, 95% CI 1.11–1.59; $p = 0.002$) with overall low heterogeneity. However, all trials were non-blinded and reported incomplete outcome measures, and were therefore considered to have a high risk of bias.[189] Furthermore, non-standard measures of clinical and endoscopic activity were used, thus greatly limiting the conclusions.

Acupuncture versus moxibustion

Moxibustion and e-AP were compared as separate treatments in a randomized study of CD patients in sustained remission. Thirty-six patients were randomly assigned to e-AP or moxa treatment over 12 weeks. In both arms there was a significant reduction of CDAI and a significant increase in the Inflammatory Bowel Disease Questionnaire (IBDQ); no significant difference was seen between both interventions.[190]

Acupuncture combined with moxibustion

The efficacy and safety of AP with moxibustion were evaluated in patients with mild-to-moderate CD; 92 subjects were randomly assigned to receive either active treatment (HPM with AP) or placebo (wheat-bran-partitioned moxa combined with superficial needle application in non-acupoints) over 12 weeks. Both groups had a significant reduction in the CDAI and IBDQ at week 12, which was significantly greater in the active treatment arm ($p < 0.001$). Patients in the active treatment group also showed a significant improvement in haemoglobin ($p = 0.026$), CRP levels ($p = 0.008$), and histopathological scores ($p = 0.029$) when compared with placebo. No significant difference was found in endoscopy.[191]

Another randomized, single-blind trial evaluated the efficacy of the combined methods in reducing CDAI after 4 weeks of treatment. Patients with mild-to-moderate CD were randomly assigned to receive 10 AP sessions over 4 weeks or sham AP. All patients in the AP arm were treated with Artemisia Moxa. Fifty-one patients were treated (27 in the active arm and 24 in the control arm). While CDAI reduction was significantly higher in the treatment arm ($p = 0.003$), the overall remission rates were not statistically different between the two arms. QoL was improved in both arms although the difference did not reach statistical significance ($p = 0.064$).[192]

Two large studies assessed the efficacy of AP combined with moxibustion in UC.[193,194] In one study, 121 patients were randomly assigned to receive either AP (N = 76) or SASP 1 to 2 g four times/day (N = 45) over a period of 20 to 60 days. In the intervention group, 59% of patients entered remission as compared with 39% of patients in the control group. Low-quality trial design affected the validity of these results.[193] In another study on 123 patients with mild-to-moderate UC, HPM with AP was compared with sham intervention (bran-partition moxibustion).[194] A significant improvement (defined as disappearance of clinical symptoms and normal colonic mucosa by sigmoidoscopy) was observed in 52.5% of patients treated with HPM versus 24.5% of patients that received sham intervention. No baseline description of patient features was provided (such as extent of colitis, Mayo score, concomitant therapies during the trial), making the results difficult to interpret.[194] In another small RCT in mild-to-moderate UC, 29 patients were randomly assigned to receive AP plus moxibustion or sham AP for 5 weeks. Disease activity was measured by the Colitis Activity Index (CAI) and QoL with IBDQ and a 10-point VAS. The treatment group showed a significant decrease in CAI after treatment ($p < 0.001$) and the benefit was maintained throughout the 16-week follow-up ($p < 0.001$). Although patients in the control group showed an improvement in disease activity, treatment was significantly superior ($p = 0.048$). In the treatment group, CAI was statistically lower than that at baseline ($p < 0.001$). QoL was improved in both groups.[195]

Finally, a meta-analysis examined the clinical efficacy of AP and/or moxibustion compared with SASP for the treatment of UC.[196] The overall efficacy of AP alone, moxibustion alone, or AP combined with moxibustion was greater than the efficacy of SASP (RR 5.42, 95% CI 3.38–8.68; $p < 0.0001$). However, the trials were underpowered and were mostly of low quality with subjective assessments of efficacy.[196] Additionally, true blinding was questioned to be even possible, as the acupuncturist always knows if the needle is inserted in an acupoint or not. Moreover, needle insertion can lead to nonspecific physiological responses and this could explain why in some studies an improvement was also obtained with sham acupuncture.[197]

In summary, the low quality of the published studies, even if with positive results, precludes any valid conclusion and recommendations.

b. Chiropractic treatment and Osteopathy

Current Practice Position 5.2

There is minimal evidence on the efficacy of chiropractic and osteopathy in the management of active CD

Chiropractic and osteopathy are two different types of CAM. Chiropractic treatment involves manual therapy, usually spinal manipulation therapy, but also

manipulations of other joints and soft tissues. Osteopathy involves massage, stretching, pressure, and mobilization of various tissues or organs.[198,199] A summary of the major studies on chiropractic and osteopathy can be found in Supplementary Table 2.

In a longitudinal, population-based study of health outcomes in an IBD cohort, among patients that used CAM, 14% used chiropractic treatament.[200,201] In a study from Sweden, 5.4% of IBD patients made use of chiropractic therapy compared with 5.7% of the normal population.[202]

There is limited data on the use and benefit of chiropractic and osteopathy as CAM in IBD, with only two randomized trials published. In a single-blind study, CD patients in remission were randomised into two groups. The aim of the study was to determine if there was an improvement in IBDQ score following visceral osteopathic treatment. Fourteen patients received visceral osteopathic technique at the root of the mesentery. The root of the mesentery gives rise to the mesentery of the small intestine and is the region connected to the structures in front of the vertebral column. The control group (N=13) did not receive any osteopathic treatment and had virtual manipulation, which consisted of palpation of the small intestine and colon without action on the vasculature and innervations. Change in QoL was assessed using the IBDQ. The IBDQ score increased significantly ($p < 0.001$) in the group treated with osteopathy; no significant change was observed in the control group ($p = 0.22$).[199] In another study, 38 CD patients who were in remission receiving infliximab were randomly assigned 2:1 to receive osteopathic or sham therapy at 15, 30, and 45 days after infliximab infusion. The severity of IBS-like symptoms was significantly reduced in patients receiving osteopathy ($p = 0.01$, $p = 0.04$, and $p = 0.05$ at day 30, 45, and 60, respectively).[203]

There are currently no published studies evaluating chiropractic and osteopathy in patients with UC or IBDU.

c. Exercise

Current Practice Position 5.3

Exercise can have beneficial effects on overall health, physical well-being, perceived stress, and QoL of IBD patients. There is promising but limited evidence on the role of exercise both in protection from IBD development and in disease management

Regular exercise exerts anti-inflammatory effects, which may be mediated through a reduction in visceral fat mass (with a consequent decreased release of adipokines) and the induction of an anti-inflammatory environment.[204,205]

In a retrospective database analysis, a sedentary occupation was associated with a two-fold increase in IBD incidence.[206] In two large prospective female cohorts, physical activity was inversely associated with risk of CD but not of UC.[207] Compared with women with low physical activity, the multivariate adjusted hazard ratio (HR) of CD among women with very high physical activity was 0.64 (95% CI 0.44–0.94).[207] Active women with at least a 27 metabolic equivalent task (MET) hours/week of physical activity had a 44% reduction (HR 0.56, 95% CI 0.37–0.84) in risk of developing CD compared with sedentary women with <3 MET hours/week.[207] In a case-control study the RR of CD was inversely related to regular physical activity (weekly exercise, RR 0.6, 95% CI 0.4–0.9; daily exercise, RR 0.5, 95% CI 0.3–0.9).[208] Furthermore, in a recent meta-analysis it was demonstrated that physical activity has a protective effect against developing CD.[209] No significant inverse association between physical activity and UC was observed.

Exercise could be used in the treatment of IBD either for its anti-inflammatory potential or for symptom relief.[210] Several studies have been performed on IBD patients (Table 2)[179,207,208,211-216] and have shown that exercise could be beneficial via a positive effect on QoL. However, these studies were limited by small sample size. In the largest study to date, 117 CD patients in remission where randomized to either a low-impact exercise program or no prescribed exercise. The primary endpoint was bone mineral density (g/cm^2) measured at baseline and at 12 months at the hip and spine (L2–L4) by dual-energy x-ray absorptiometry. This study revealed that exercise was associated with increasing bone mineral density. Effects on disease activity were not measured.[211] A prospective study[216] on CD patients in remission (CDAI < 150) revealed that those with higher exercise levels were significantly less likely to develop active disease at 6 months. In UC patients in remission, those with higher exercise levels were also less likely, albeit non-significantly, to develop active disease at 6 months.

Data are lacking regarding the intensity and type of exercise. Furthermore, for active disease there is a possibility that exercise could exacerbate symptoms, as more rigorous exercise may cause gastrointestinal symptoms such as bloating, cramps, and urgency to defecate.[217] A trial assessing two exercise regimens in adults with inactive or mildly active CD is currently underway.[218] New technology, including next-generation wearable physical activity trackers, could potentially improve exercise studies and might be used to promote physical activity[219] in IBD patients.

7. CONCLUSION

Various types of CAMs and psychotherapy interventions are available. However, for most of them, the lack of rigorously conducted trials has hampered their use. Regarding psychotherapy and mind-body interventions, a positive effect on quality of life has been reported; effect in disease activity is less clear. Physicians should be

informed about the evidence behind most frequently used CAMs and be ready to provide advice to their patients. Further research is needed before strong recommendations can be made.

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REFERENCES

1. Gilardi D, Fiorino G, Genua M, Allocca M, Danese S. Complementary and alternative medicine in inflammatory bowel diseases: What is the future in the field of herbal medicine? *Expert Rev Gastroenterol Hepatol* 2014;**8**:835-46.
2. Romberg-Camps MJ, Bol Y, Dagnelie PC*, et al.* Fatigue and health-related quality of life in inflammatory bowel disease: Results from a population-based study in the netherlands: The ibd-south limburg cohort. *Inflammatory bowel diseases* 2010;**16**:2137-47.
3. Targownik LE, Sexton KA, Bernstein MT*, et al.* The relationship among perceived stress, symptoms, and inflammation in persons with inflammatory bowel disease. *The American journal of gastroenterology* 2015;**110**:1001-12; quiz 13.
4. Naftali T, Lev LB, Yablecovitch D, Half E, Konikoff FM. Treatment of crohn's disease with cannabis: An observational study. *The Israel Medical Association journal : IMAJ* 2011;**13**:455-8.
5. Naftali T, Bar-Lev Schleider L, Dotan I*, et al.* Cannabis induces a clinical response in patients with crohn's disease: A prospective placebo-controlled study. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2013;**11**:1276-80 e1.
6. Omer B, Krebs S, Omer H, Noor TO. Steroid-sparing effect of wormwood (artemisia absinthium) in crohn's disease: A double-blind placebo-controlled study. *Phytomedicine* 2007;**14**:87-95.
7. Krebs S, Omer TN, Omer B. Wormwood (artemisia absinthium) suppresses tumour necrosis factor alpha and accelerates healing in patients with crohn's disease - a controlled clinical trial. *Phytomedicine* 2010;**17**:305-9.

8. Holtmeier W, Zeuzem S, Preiss J*, et al.* Randomized, placebo-controlled, double-blind trial of boswellia serrata in maintaining remission of crohn's disease: Good safety profile but lack of efficacy. *Inflammatory bowel diseases* 2011;**17**:573-82.
9. Kanazawa A, Sako M, Takazoe M*, et al.* Daikenchuto, a traditional japanese herbal medicine, for the maintenance of surgically induced remission in patients with crohn's disease: A retrospective analysis of 258 patients. *Surgery today* 2014;**44**:1506-12.
10. Ren J, Tao Q, Wang X, Wang Z, Li J. Efficacy of t2 in active crohn's disease: A prospective study report. *Digestive diseases and sciences* 2007;**52**:1790-7.
11. Ren J, Wu X, Liao N*, et al.* Prevention of postoperative recurrence of crohn's disease: Tripterygium wilfordii polyglycoside versus mesalazine. *The Journal of international medical research* 2013;**41**:176-87.
12. Sun J, Shen X, Dong J*, et al.* Tripterygium wilfordii hook f as maintenance treatment for crohn's disease. *The American journal of the medical sciences* 2015;**350**:345-51.
13. Zhu W, Li Y, Gong J*, et al.* Tripterygium wilfordii hook. F. Versus azathioprine for prevention of postoperative recurrence in patients with crohn's disease: A randomized clinical trial. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2015;**47**:14-9.
14. Singla V, Pratap Mouli V, Garg SK*, et al.* Induction with ncb-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis - a randomized, placebo-controlled, pilot study. *Journal of Crohn's & colitis* 2014;**8**:208-14.
15. Lang A, Salomon N, Wu JCY*, et al.* Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. *Clinical Gastroenterology and Hepatology* 2015;**13**:1444-9.e1.
16. Langmead L, Feakins RM, Goldthorpe S*, et al.* Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. *Alimentary pharmacology & therapeutics* 2004;**19**:739-47.
17. Tang T, Targan SR, Li ZS*, et al.* Randomised clinical trial: Herbal extract hmpl-004 in active ulcerative colitis - a double-blind comparison with sustained release mesalazine. *Alimentary pharmacology & therapeutics* 2011;**33**:194-202.
18. Sandborn WJ, Targan SR, Byers VS*, et al.* Andrographis paniculata extract (hmpl-004) for active ulcerative colitis. *The American journal of gastroenterology* 2013;**108**:90-8.
19. Kamali M, Tavakoli H, Khodadoost M*, et al.* Efficacy of the punica granatum peels aqueous extract for symptom management in ulcerative colitis patients. A randomized, placebo-controlled, clinical trial. *Complementary therapies in clinical practice* 2015;**21**:141-6.

20. Ben-Arye E, Goldin E, Wengrower D*, et al.* Wheat grass juice in the treatment of active distal ulcerative colitis: A randomized double-blind placebo-controlled trial. *Scandinavian journal of gastroenterology* 2002;**37**:444-9.
21. Tong ZQ, Yang B, Chen BY, Zhao ML. A multi-center, randomized, single-blind, controlled clinical study on the efficacy of composite sophora colon-soluble capsules in treating ulcerative colitis. *Chinese journal of integrative medicine* 2010;**16**:486-92.
22. Hanai H, Iida T, Takeuchi K*, et al.* Curcumin maintenance therapy for ulcerative colitis: Randomized, multicenter, double-blind, placebo-controlled trial. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2006;**4**:1502-6.
23. Langhorst J, Varnhagen I, Schneider SB*, et al.* Randomised clinical trial: A herbal preparation of myrrh, chamomile and coffee charcoal compared with mesalazine in maintaining remission in ulcerative colitis--a double-blind, double-dummy study. *Alimentary pharmacology & therapeutics* 2013;**38**:490-500.
24. Rastegarpanah M, Malekzadeh R, Vahedi H*, et al.* A randomized, double blinded, placebo-controlled clinical trial of silymarin in ulcerative colitis. *Chinese journal of integrative medicine* 2015;**21**:902-6.
25. Johari S, Gandhi T. A randomized single blind parallel group study comparing monoherbal formulation containing holarrhena antidysenterica extract with mesalamine in chronic ulcerative colitis patients. *Ancient science of life* 2016;**36**:19-27.
26. Ling XH, Yu X, Kong DJ*, et al.* Treatment of inflammatory bowel disease with chinese drugs administered by both oral intake and retention enema. *Chinese journal of integrative medicine* 2010;**16**:222-8.
27. Salaga M, Zatorski H, Sobczak M, Chen C, Fichna J. Chinese herbal medicines in the treatment of ibd and colorectal cancer: A review. *Current treatment options in oncology* 2014;**15**:405-20.
28. Ling W, Li Y, Jiang W, Sui Y, Zhao HL. Common mechanism of pathogenesis in gastrointestinal diseases implied by consistent efficacy of single chinese medicine formula: A prisma-compliant systematic review and meta-analysis. *Medicine* 2015;**94**:e1111.
29. Teschke R, Wolff A, Frenzel C, Eickhoff A, Schulze J. Herbal traditional chinese medicine and its evidence base in gastrointestinal disorders. *World journal of gastroenterology* 2015;**21**:4466-90.
30. Biedermann L, Mwinyi J, Scharl M*, et al.* Bilberry ingestion improves disease activity in mild to moderate ulcerative colitis - an open pilot study. *Journal of Crohn's & colitis* 2013;**7**:271-9.

31. Huber R, Ditfurth AV, Amann F*, et al.* Tormentil for active ulcerative colitis: An open-label, dose-escalating study. *Journal of clinical gastroenterology* 2007;**41**:834-8.
32. Patel KB, Patel M, Mehta CS, Gupta S, Kessler CS. Ayurvedic management of ulcerative colitis--a non-randomized observational clinical study. *Forschende Komplementarmedizin (2006)* 2013;**20**:144-7.
33. Aghdassi E, Wendland BE, Steinhart AH*, et al.* Antioxidant vitamin supplementation in crohn's disease decreases oxidative stress. A randomized controlled trial. *The American journal of gastroenterology* 2003;**98**:348-53.
34. Bartels LE, Jorgensen SP, Agnholt J*, et al.* 1,25-dihydroxyvitamin d3 and dexamethasone increase interleukin-10 production in cd4+ t cells from patients with crohn's disease. *International immunopharmacology* 2007;**7**:1755-64.
35. Miheller P, Muzes G, Hritz I*, et al.* Comparison of the effects of 1,25 dihydroxyvitamin d and 25 hydroxyvitamin d on bone pathology and disease activity in crohn's disease patients. *Inflammatory bowel diseases* 2009;**15**:1656-62.
36. Jorgensen SP, Agnholt J, Glerup H*, et al.* Clinical trial: Vitamin d3 treatment in crohn's disease - a randomized double-blind placebo-controlled study. *Alimentary pharmacology & therapeutics* 2010;**32**:377-83.
37. Kumari M, Khazai NB, Ziegler TR*, et al.* Vitamin d-mediated calcium absorption in patients with clinically stable crohn's disease: A pilot study. *Molecular nutrition & food research* 2010;**54**:1085-91.
38. Verway M, Behr MA, White JH. Vitamin d, nod2, autophagy and crohn's disease. *Expert review of clinical immunology* 2010;**6**:505-8.
39. Kelly P, Suibhne TN, O'Morain C, O'Sullivan M. Vitamin d status and cytokine levels in patients with crohn's disease. *International journal for vitamin and nutrition research Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung Journal international de vitaminologie et de nutrition* 2011;**81**:205-10.
40. Yang L, Weaver V, Smith JP*, et al.* Therapeutic effect of vitamin d supplementation in a pilot study of crohn's patients. *Clinical and translational gastroenterology* 2013;**4**:e33.
41. Augustine MV, Leonard MB, Thayu M*, et al.* Changes in vitamin d-related mineral metabolism after induction with anti-tumor necrosis factor-alpha therapy in crohn's disease. *The Journal of clinical endocrinology and metabolism* 2014;**99**:E991-8.
42. Basson A. Vitamin d and crohn's disease in the adult patient: A review. *JPEN Journal of parenteral and enteral nutrition* 2014;**38**:438-58.

43. Ghaly S, Lawrance I. The role of vitamin d in gastrointestinal inflammation. *Expert Rev Gastroenterol Hepatol* 2014;**8**:909-23.
44. Hlavaty T, Krajcovicova A, Koller T*, et al.* Higher vitamin d serum concentration increases health related quality of life in patients with inflammatory bowel diseases. *World journal of gastroenterology* 2014;**20**:15787-96.
45. Zator ZA, Cantu SM, Konijeti GG*, et al.* Pretreatment 25-hydroxyvitamin d levels and durability of anti-tumor necrosis factor-alpha therapy in inflammatory bowel diseases. *JPEN Journal of parenteral and enteral nutrition* 2014;**38**:385-91.
46. Hlavaty T, Krajcovicova A, Payer J. Vitamin d therapy in inflammatory bowel diseases: Who, in what form, and how much? *Journal of Crohn's & colitis* 2015;**9**:198-209.
47. Raftery T, Martineau AR, Greiller CL*, et al.* Effects of vitamin d supplementation on intestinal permeability, cathelicidin and disease markers in crohn's disease: Results from a randomised double-blind placebo-controlled study. *United European gastroenterology journal* 2015;**3**:294-302.
48. Barbalho SM, Bechara MD, de Alvares Goulart R*, et al.* Reflections about inflammatory bowel disease and vitamins a and d. *Journal of medicinal food* 2016;**19**:1105-10.
49. Kojecky V, Adamikova A, Klimek P. Vitamin d supplementation in inflammatory bowel disease: The role of dosage and patient compliance. *Bratislavske lekarske listy* 2016;**117**:148-51.
50. Reich KM, Fedorak RN, Madsen K, Kroeker KI. Role of vitamin d in infliximab-induced remission in adult patients with crohn's disease. *Inflammatory bowel diseases* 2016;**22**:92-9.
51. Sadeghian M, Saneei P, Siassi F, Esmaillzadeh A. Vitamin d status in relation to crohn's disease: Meta-analysis of observational studies. *Nutrition (Burbank, Los Angeles County, Calif)* 2016;**32**:505-14.
52. Santos-Antunes J, Nunes AC, Lopes S, Macedo G. The relevance of vitamin d and antinuclear antibodies in patients with inflammatory bowel disease under anti-tnf treatment: A prospective study. *Inflammatory bowel diseases* 2016;**22**:1101-6.
53. Sharifi A, Hosseinzadeh-Attar MJ, Vahedi H, Nedjat S. A randomized controlled trial on the effect of vitamin d3 on inflammation and cathelicidin gene expression in ulcerative colitis patients. *Saudi journal of gastroenterology : official journal of the Saudi Gastroenterology Association* 2016;**22**:316-23.
54. Abdo J, Rai V, Agrawal DK. Interplay of immunity and vitamin d: Interactions and implications with current ibd therapy. *Current medicinal chemistry* 2017;**24**:852-67.

55. Garg M, Rosella O, Rosella G*, et al.* Evaluation of a 12-week targeted vitamin d supplementation regimen in patients with active inflammatory bowel disease. *Clinical nutrition (Edinburgh, Scotland)* 2017.
56. Narula N, Cooray M, Anglin R*, et al.* Impact of high-dose vitamin d3 supplementation in patients with crohn's disease in remission: A pilot randomized double-blind controlled study. *Digestive diseases and sciences* 2017;**62**:448-55.
57. Costantini A, Pala MI. Thiamine and fatigue in inflammatory bowel diseases: An open-label pilot study. *Journal of alternative and complementary medicine (New York, NY)* 2013;**19**:704-8.
58. Mortimore M, Florin TH. A role for b(1)(2) in inflammatory bowel disease patients with suppurative dermatoses? An experience with high dose vitamin b(1)(2) therapy. *Journal of Crohn's & colitis* 2010;**4**:466-70.
59. Pan Y, Liu Y, Guo H*, et al.* Associations between folate and vitamin b12 levels and inflammatory bowel disease: A meta-analysis. *Nutrients* 2017;**9**.
60. O'Connor EM, Grealy G, McCarthy J*, et al.* Effect of phylloquinone (vitamin k1) supplementation for 12 months on the indices of vitamin k status and bone health in adult patients with crohn's disease. *The British journal of nutrition* 2014;**112**:1163-74.
61. Holick MF. Vitamin d deficiency. *N Engl J Med* 2007;**357**:266-81.
62. Cantorna MT, Munsick C, Bemiss C, Mahon BD. 1,25-dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease. *J Nutr* 2000;**130**:2648-52.
63. Garg M, Rosella O, Rosella G*, et al.* Evaluation of a 12-week targeted vitamin d supplementation regimen in patients with active inflammatory bowel disease. *Clinical nutrition (Edinburgh, Scotland)* 2018;**37**:1375-82.
64. Nowak JK, Grzybowska-Chlebowczyk U, Landowski P*, et al.* Prevalence and correlates of vitamin k deficiency in children with inflammatory bowel disease. *Sci Rep* 2014;**4**:4768.
65. Shea MK, Booth SL, Massaro JM*, et al.* Vitamin k and vitamin d status: Associations with inflammatory markers in the framingham offspring study. *Am J Epidemiol* 2008;**167**:313-20.
66. Sigall-Boneh R, Levine A, Lomer M*, et al.* Research gaps in diet and nutrition in inflammatory bowel disease. A topical review by d-ecco working group [dietitians of ecco]. *Journal of Crohn's & colitis* 2017;**11**:1407-19.
67. 1, Wedlake L, Slack N, Andreyev HJ, Whelan K. Fiber in the treatment and maintenance of inflammatory bowel disease: A systematic review of randomized controlled trials. *Inflammatory bowel diseases* 2014;**20**:576-86.

68. Luhrs H, Gerke T, Muller JG*, et al.* Butyrate inhibits nf-kappab activation in lamina propria macrophages of patients with ulcerative colitis. *Scandinavian journal of gastroenterology* 2002;**37**:458-66.
69. Middleton SJ, Naylor S, Woolner J, Hunter JO. A double-blind, randomized, placebo-controlled trial of essential fatty acid supplementation in the maintenance of remission of ulcerative colitis. *Alimentary pharmacology & therapeutics* 2002;**16**:1131-5.
70. Hallert C, Bjorck I, Nyman M*, et al.* Increasing fecal butyrate in ulcerative colitis patients by diet: Controlled pilot study. *Inflammatory bowel diseases* 2003;**9**:116-21.
71. Vernia P, Annese V, Bresci G*, et al.* Topical butyrate improves efficacy of 5-asa in refractory distal ulcerative colitis: Results of a multicentre trial. *European journal of clinical investigation* 2003;**33**:244-8.
72. Di Sabatino A, Morera R, Ciccocioppo R*, et al.* Oral butyrate for mildly to moderately active crohn's disease. *Alimentary pharmacology & therapeutics* 2005;**22**:789-94.
73. MacLean CH, Mojica WA, Newberry SJ*, et al.* Systematic review of the effects of n-3 fatty acids in inflammatory bowel disease. *The American journal of clinical nutrition* 2005;**82**:611-9.
74. Assisi RF. Combined butyric acid/mesalazine treatment in ulcerative colitis with mild-moderate activity. Results of a multicentre pilot study. *Minerva gastroenterologica e dietologica* 2008;**54**:231-8.
75. Hamer HM, Jonkers DM, Vanhoutvin SA*, et al.* Effect of butyrate enemas on inflammation and antioxidant status in the colonic mucosa of patients with ulcerative colitis in remission. *Clinical nutrition (Edinburgh, Scotland)* 2010;**29**:738-44.
76. Uchiyama K, Nakamura M, Odahara S*, et al.* N-3 polyunsaturated fatty acid diet therapy for patients with inflammatory bowel disease. *Inflammatory bowel diseases* 2010;**16**:1696-707.
77. Mikhailova TL, Sishkova E, Poniewierka E*, et al.* Randomised clinical trial: The efficacy and safety of propionyl-l-carnitine therapy in patients with ulcerative colitis receiving stable oral treatment. *Alimentary pharmacology & therapeutics* 2011;**34**:1088-97.
78. Bassaganya-Riera J, Hontecillas R, Horne WT*, et al.* Conjugated linoleic acid modulates immune responses in patients with mild to moderately active crohn's disease. *Clinical nutrition (Edinburgh, Scotland)* 2012;**31**:721-7.
79. Bueno-Hernandez N, Sixtos-Alonso MS, Milke Garcia MDP, Yamamoto-Furusho JK. Effect of cis-palmitoleic acid supplementation on inflammation and expression of hnf4gamma, hnf4alpha and il6 in patients with ulcerative colitis. *Minerva gastroenterologica e dietologica* 2017;**63**:257-63.

80. Benus RF, van der Werf TS, Welling GW*, et al.* Association between faecalibacterium prausnitzii and dietary fibre in colonic fermentation in healthy human subjects. *The British journal of nutrition* 2010;**104**:693-700.
81. Wong C, Harris PJ, Ferguson LR. Potential benefits of dietary fibre intervention in inflammatory bowel disease. *International journal of molecular sciences* 2016;**17**.
82. Fernandez-Banares F, Hinojosa J, Sanchez-Lombrana JL*, et al.* Randomized clinical trial of plantago ovata seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish group for the study of crohn's disease and ulcerative colitis (geteccu). *The American journal of gastroenterology* 1999;**94**:427-33.
83. Faghfoori Z, Shakerhosseini R, Navai L*, et al.* Effects of an oral supplementation of germinated barley foodstuff on serum crp level and clinical signs in patients with ulcerative colitis. *Health promotion perspectives* 2014;**4**:116-21.
84. Hanai H, Kanauchi O, Mitsuyama K*, et al.* Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. *International journal of molecular medicine* 2004;**13**:643-7.
85. Kanauchi O, Suga T, Tochihara M*, et al.* Treatment of ulcerative colitis by feeding with germinated barley foodstuff: First report of a multicenter open control trial. *Journal of gastroenterology* 2002;**37 Suppl 14**:67-72.
86. Chermesh I, Tamir A, Reshef R*, et al.* Failure of synbiotic 2000 to prevent postoperative recurrence of crohn's disease. *Digestive diseases and sciences* 2007;**52**:385-9.
87. Steed H, Macfarlane GT, Blackett KL*, et al.* Clinical trial: The microbiological and immunological effects of synbiotic consumption - a randomized double-blind placebo-controlled study in active crohn's disease. *Alimentary pharmacology & therapeutics* 2010;**32**:872-83.
88. Benjamin JL, Hedin CR, Koutsoumpas A*, et al.* Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active crohn's disease. *Gut* 2011;**60**:923-9.
89. Ritchie JK, Wadsworth J, Lennard-Jones JE, Rogers E. Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in crohn's disease. *Br Med J (Clin Res Ed)* 1987;**295**:517-20.
90. Stange EF, Schmid U, Fleig WE, Ditschuneit H. [exclusion diet in crohn disease: A controlled, randomized study]. *Z Gastroenterol* 1990;**28**:561-4.
91. Lindsay JO, Whelan K, Stagg AJ*, et al.* Clinical, microbiological, and immunological effects of fructo-oligosaccharide in patients with crohn's disease. *Gut* 2006;**55**:348-55.
92. Joossens M, De Preter V, Ballet V*, et al.* Effect of oligofructose-enriched inulin (of-in) on bacterial composition and disease activity of patients with crohn's disease: Results from a double-blinded randomised controlled trial. *Gut* 2012;**61**:958.

93. Grimstad T, Berge RK, Bohov P*, et al.* Salmon diet in patients with active ulcerative colitis reduced the simple clinical colitis activity index and increased the anti-inflammatory fatty acid index--a pilot study. *Scandinavian journal of clinical and laboratory investigation* 2011;**71**:68-73.

94. Lev-Tzion R, Griffiths AM, Leder O, Turner D. Omega 3 fatty acids (fish oil) for maintenance of remission in crohn's disease. *The Cochrane database of systematic reviews* 2014:CD006320.

95. Grimstad T, Bjorndal B, Cacabelos D*, et al.* A salmon peptide diet alleviates experimental colitis as compared with fish oil. *Journal of nutritional science* 2013;**2**:e2.

96. Barbosa DS, Cecchini R, El Kadri MZ*, et al.* Decreased oxidative stress in patients with ulcerative colitis supplemented with fish oil omega-3 fatty acids. *Nutrition (Burbank, Los Angeles County, Calif)* 2003;**19**:837-42.

97. Trebble TM, Stroud MA, Wootton SA*, et al.* High-dose fish oil and antioxidants in crohn's disease and the response of bone turnover: A randomised controlled trial. *The British journal of nutrition* 2005;**94**:253-61.

98. Nielsen AA, Jorgensen LG, Nielsen JN*, et al.* Omega-3 fatty acids inhibit an increase of proinflammatory cytokines in patients with active crohn's disease compared with omega-6 fatty acids. *Alimentary pharmacology & therapeutics* 2005;**22**:1121-8.

99. Eivindson M, Gronbaek H, Nielsen JN*, et al.* Insulin-like growth factors (igfs) and igf binding proteins in active crohn's disease treated with omega-3 or omega-6 fatty acids and corticosteroids. *Scandinavian journal of gastroenterology* 2005;**40**:1214-21.

100. Turner D, Shah PS, Steinhart AH, Zlotkin S, Griffiths AM. Maintenance of remission in inflammatory bowel disease using omega-3 fatty acids (fish oil): A systematic review and meta-analyses. *Inflammatory bowel diseases* 2011;**17**:336-45.

101. Turner D, Zlotkin SH, Shah PS, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in crohn's disease. *The Cochrane database of systematic reviews* 2009:CD006320.

102. Feagan BG, Sandborn WJ, Mittmann U*, et al.* Omega-3 free fatty acids for the maintenance of remission in crohn disease: The epic randomized controlled trials. *Jama* 2008;**299**:1690-7.

103. 1, Cabre E, Manosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases - a systematic review. *The British journal of nutrition* 2012;**107 Suppl 2**:S240-52.

104. Seidner DL, Lashner BA, Brzezinski A*, et al.* An oral supplement enriched with fish oil, soluble fiber, and antioxidants for corticosteroid sparing in ulcerative colitis: A randomized, controlled trial. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2005;**3**:358-69.

105. Bjorkkjaer T, Brunborg LA, Arslan G*, et al.* Reduced joint pain after short-term duodenal administration of seal oil in patients with inflammatory bowel disease: Comparison with soy oil. *Scandinavian journal of gastroenterology* 2004;**39**:1088-94.
106. Arslan G, Brunborg LA, Froyland L*, et al.* Effects of duodenal seal oil administration in patients with inflammatory bowel disease. *Lipids* 2002;**37**:935-40.
107. Brunborg LA, Madland TM, Lind RA*, et al.* Effects of short-term oral administration of dietary marine oils in patients with inflammatory bowel disease and joint pain: A pilot study comparing seal oil and cod liver oil. *Clinical nutrition (Edinburgh, Scotland)* 2008;**27**:614-22.
108. Derwa Y, Gracie DJ, Hamlin PJ, Ford AC. Systematic review with meta-analysis: The efficacy of probiotics in inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2017;**46**:389-400.
109. Malchow HA. Crohn's disease and escherichia coli. A new approach in therapy to maintain remission of colonic crohn's disease? *Journal of clinical gastroenterology* 1997;**25**:653-8.
110. Schultz M, Timmer A, Herfarth HH*, et al.* Lactobacillus gg in inducing and maintaining remission of crohn's disease. *BMC gastroenterology* 2004;**4**:5.
111. Willert RP, Peddi KK, Ombiga J, Bampton PA, Lawrance IC. Randomised, double-blinded, placebo-controlled study of vsl#3 versus placebo in the maintenance of remission in crohns disease. *Gastroenterology* 2010;**138**:S-517-S-8.
112. Bourreille A, Cadiot G, Le Dreau G*, et al.* Saccharomyces boulardii does not prevent relapse of crohn's disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2013;**11**:982-7.
113. Fedorak RN, Feagan BG, Hotte N*, et al.* The probiotic vsl#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for crohn's disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2015;**13**:928-35 e2.
114. Marteau P, Lemann M, Seksik P*, et al.* Ineffectiveness of lactobacillus johnsonii la1 for prophylaxis of postoperative recurrence in crohn's disease: A randomised, double blind, placebo controlled getaid trial. *Gut* 2006;**55**:842-7.
115. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for crohn's disease: A randomised controlled trial with lactobacillus gg. *Gut* 2002;**51**:405-9.
116. Van Gossum A, Dewit O, Louis E*, et al.* Multicenter randomized-controlled clinical trial of probiotics (lactobacillus johnsonii, la1) on early endoscopic recurrence of crohn's disease after lleo-caecal resection. *Inflammatory bowel diseases* 2007;**13**:135-42.

117. Kato K, Mizuno S, Umesaki Y*, et al.* Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Alimentary pharmacology & therapeutics* 2004;**20**:1133-41.
118. Matthes H, Krummenerl T, Giensch M, Wolff C, Schulze J. Clinical trial: Probiotic treatment of acute distal ulcerative colitis with rectally administered escherichia coli nissle 1917 (ecn). *BMC complementary and alternative medicine* 2010;**10**:13.
119. Ng SC, Plamondon S, Kamm MA*, et al.* Immunosuppressive effects via human intestinal dendritic cells of probiotic bacteria and steroids in the treatment of acute ulcerative colitis. *Inflammatory bowel diseases* 2010;**16**:1286-98.
120. Petersen AM, Mirsepasi H, Halkjaer SI*, et al.* Ciprofloxacin and probiotic escherichia coli nissle add-on treatment in active ulcerative colitis: A double-blind randomized placebo controlled clinical trial. *Journal of Crohn's & colitis* 2014;**8**:1498-505.
121. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic escherichia coli versus mesalazine for the treatment of ulcerative colitis: A randomised trial. *Lancet (London, England)* 1999;**354**:635-9.
122. Sood A, Midha V, Makharia GK*, et al.* The probiotic preparation, vsl#3 induces remission in patients with mild-to-moderately active ulcerative colitis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2009;**7**:1202-9, 9 e1.
123. Tamaki H, Nakase H, Inoue S*, et al.* Efficacy of probiotic treatment with bifidobacterium longum 536 for induction of remission in active ulcerative colitis: A randomized, double-blinded, placebo-controlled multicenter trial. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society* 2016;**28**:67-74.
124. Tursi A, Brandimarte G, Papa A*, et al.* Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic vsl#3 as adjunctive to a standard pharmaceutical treatment: A double-blind, randomized, placebo-controlled study. *The American journal of gastroenterology* 2010;**105**:2218-27.
125. Cui HH, Chen CL, Wang JD*, et al.* Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. *World journal of gastroenterology* 2004;**10**:1521-5.
126. Kruis W, Fric P, Pokrotnieks J*, et al.* Maintaining remission of ulcerative colitis with the probiotic escherichia coli nissle 1917 is as effective as with standard mesalazine. *Gut* 2004;**53**:1617-23.

127. Kruis W, Schutz E, Fric P*, et al.* Double-blind comparison of an oral escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. *Alimentary pharmacology & therapeutics* 1997;**11**:853-8.
128. Wildt S, Nordgaard I, Hansen U, Brockmann E, Rumessen JJ. A randomised double-blind placebo-controlled trial with lactobacillus acidophilus la-5 and bifidobacterium animalis subsp. Lactis bb-12 for maintenance of remission in ulcerative colitis. *Journal of Crohn's & colitis* 2011;**5**:115-21.
129. Yoshimatsu Y, Yamada A, Furukawa R*, et al.* Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive ulcerative colitis. *World journal of gastroenterology* 2015;**21**:5985-94.
130. Zocco MA, dal Verme LZ, Cremonini F*, et al.* Efficacy of lactobacillus gg in maintaining remission of ulcerative colitis. *Alimentary pharmacology & therapeutics* 2006;**23**:1567-74.
131. Greenley RN, Hommel KA, Nebel J*, et al.* A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. *Journal of pediatric psychology* 2010;**35**:857-69.
132. Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies revisited: A systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflammatory bowel diseases* 2016;**22**:752-62.
133. Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with inflammatory bowel disease: A systematic review. *Journal of psychosomatic research* 2016;**87**:70-80.
134. Ross SC, Strachan J, Russell RK, Wilson SL. Psychosocial functioning and health-related quality of life in paediatric inflammatory bowel disease. *Journal of pediatric gastroenterology and nutrition* 2011;**53**:480-8.
135. Loftus EV, Jr., Guerin A, Yu AP*, et al.* Increased risks of developing anxiety and depression in young patients with crohn's disease. *The American journal of gastroenterology* 2011;**106**:1670-7.
136. Walker JR, Ediger JP, Graff LA*, et al.* The manitoba ibd cohort study: A population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *American Journal of Gastroenterology* 2008;**103**:1989-97.
137. Camara RJ, Ziegler R, Begre S, Schoepfer AM, von Kanel R. The role of psychological stress in inflammatory bowel disease: Quality assessment of methods of 18 prospective studies and suggestions for future research. *Digestion* 2009;**80**:129-39.

138. Timmer A, Preiss JC, Motschall E*, et al.* Psychological interventions for treatment of inflammatory bowel disease. *The Cochrane database of systematic reviews* 2011:CD006913.
139. Knowles SR, Monshat K, Castle DJ. The efficacy and methodological challenges of psychotherapy for adults with inflammatory bowel disease: A review. *Inflammatory bowel diseases* 2013;**19**:2704-15.
140. Bernstein CN, Singh S, Graff LA*, et al.* A prospective population-based study of triggers of symptomatic flares in ibd. *The American journal of gastroenterology* 2010;**105**:1994-2002.
141. Bitton A, Dobkin PL, Edwardes MD*, et al.* Predicting relapse in crohn's disease: A biopsychosocial model. *Gut* 2008;**57**:1386-92.
142. Bernstein MT, Targownik LE, Sexton KA*, et al.* Assessing the relationship between sources of stress and symptom changes among persons with ibd over time: A prospective study. 2016;**2016**:1681507.
143. van Langenberg DR, Gibson PR. Systematic review: Fatigue in inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2010;**32**:131-43.
144. Czuber-Dochan W, Ream E, Norton C. Review article: Description and management of fatigue in inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2013;**37**:505-16.
145. Kreijne J, Fuhler G, van der Woude CJ, Peppelenbosch M. Common genetic predisposition between fatigue-related syndromes and inflammatory bowel disease: A systematic review. *Journal of Crohns & Colitis* 2016;**10**:S475-S6.
146. Kreijne JE, Lie MR, Vogelaar L, van der Woude CJ. Practical guideline for fatigue management in inflammatory bowel disease. *Journal of Crohn's & colitis* 2016;**10**:105-11.
147. Grimstad T, Norheim KB. Fatigue in inflammatory bowel disease. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke* 2016;**136**:1721-4.
148. Artom M, Czuber-Dochan W, Sturt J, Norton C. Targets for health interventions for inflammatory bowel disease-fatigue. *Journal of Crohn's & colitis* 2016;**10**:860-9.
149. Graff LA, Vincent N, Walker JR*, et al.* A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflammatory bowel diseases* 2011;**17**:1882-9.
150. Grimstad T, Norheim KB, Isaksen K*, et al.* Fatigue in newly diagnosed inflammatory bowel disease. *Journal of Crohn's & colitis* 2015;**9**:725-30.
151. Norton C, Czuber-Dochan W, Bassett P*, et al.* Assessing fatigue in inflammatory bowel disease: Comparison of three fatigue scales. *Alimentary pharmacology & therapeutics* 2015;**42**:203-11.
152. Goldenberg BA, Graff LA, Clara I*, et al.* Is iron deficiency in the absence of anemia associated with fatigue in inflammatory bowel disease? *The American journal of gastroenterology* 2013;**108**:1392-7.

153. Danese S, Hoffman C, Vel S*, et al.* Anaemia from a patient perspective in inflammatory bowel disease: Results from the european federation of crohn's and ulcerative colitis association's online survey. *European journal of gastroenterology & hepatology* 2014;**26**:1385-91.
154. Geisz M, Ha C, Kappelman M*, et al.* Medication utilization and the impact of continued corticosteroid use on patient-reported outcomes in elderly patients with inflammatory bowel disease. *Inflammatory Bowel Diseases Conference: 2015 Advances in Inflammatory Bowel Diseases, Crohn's and Colitis Foundation's National Clinical and Research Conference, AIBD 2015 Orlando, FL United States Conference Start: 20151210 Conference End: 20151212 Conference Publication: (varpagings)* 2016;**22**:S16. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/830/CN-01171830/frame.html.
155. Vogelaar L, van den Berg-Emons R, Bussmann H*, et al.* Physical fitness and physical activity in fatigued and non-fatigued inflammatory bowel disease patients. *Scandinavian journal of gastroenterology* 2015;**50**:1357-67.
156. Vogelaar L, de Haar C, Aerts BR*, et al.* Fatigue in patients with inflammatory bowel disease is associated with distinct differences in immune parameters. *Clinical and experimental gastroenterology* 2017;**10**:83-90.
157. van Erp S, Ercan E, Breedveld P*, et al.* Cerebral magnetic resonance imaging in quiescent crohn's disease patients with fatigue. *World journal of gastroenterology* 2017;**23**:1018-29.
158. McNelly A, Nathan I, Monti M*, et al.* Inflammatory bowel disease and fatigue: The effect of physical activity and/or omega-3 supplementation. *Journal of Crohns & Colitis* 2016;**10**:S370-S1.
159. Vogelaar L, van't Spijker A, Timman R*, et al.* Fatigue management in patients with ibd: A randomised controlled trial. *Gut* 2014;**63**:911-8. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/720/CN-00993720/frame.html.
160. Garcia-Vega E, Fernandez-Rodriguez C. A stress management programme for crohn's disease. *Behaviour research and therapy* 2004;**42**:367-83.
161. Abdalla MI, Sandler RS, Kappelman MD*, et al.* Prevalence and impact of inflammatory bowel disease-irritable bowel syndrome on patient-reported outcomes in ccfa partners. *Inflammatory bowel diseases* 2017;**23**:325-31.
162. Diederen K, Hoekman DR, Hummel TZ*, et al.* The prevalence of irritable bowel syndrome-type symptoms in paediatric inflammatory bowel disease, and the relationship with biochemical markers of disease activity. *Alimentary pharmacology & therapeutics* 2016;**44**:181-8.

163. Watson KL, Jr., Kim SC, Boyle BM, Saps M. The prevalence and impact of functional abdominal pain disorders in children with inflammatory bowel diseases (ibd-fapd). *Journal of pediatric gastroenterology and nutrition* 2016.
164. Zimmerman LA, Srinath AI, Goyal A*, et al.* The overlap of functional abdominal pain in pediatric crohn's disease. *Inflammatory bowel diseases* 2013;**19**:826-31.
165. Piche T, Ducrotte P, Sabate JM*, et al.* Impact of functional bowel symptoms on quality of life and fatigue in quiescent crohn disease and irritable bowel syndrome. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 2010;**22**:626-e174.
166. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: Systematic review and meta-analysis. *The American journal of gastroenterology* 2012;**107**:1474-82.
167. Ranjbaran Z, Keefer L, Farhadi A*, et al.* Impact of sleep disturbances in inflammatory bowel disease. *Journal of Gastroenterology and Hepatology* 2007;**22**:1748-53.
168. Poitras P, Gougeon A, Binn M, Bouin M. Extra digestive manifestations of irritable bowel syndrome: Intolerance to drugs? *Digestive diseases and sciences* 2008;**53**:2168-76.
169. Uemura R, Fujiwara Y, Iwakura N*, et al.* Sleep disturbances in japanese patients with inflammatory bowel disease and their impact on disease flare. *Springerplus* 2016;**5**:1792.
170. Pirinen T, Kolho KL, Simola P, Ashorn M, Aronen ET. Parent and self-report of sleep-problems and daytime tiredness among adolescents with inflammatory bowel disease and their population-based controls. *Sleep* 2010;**33**:1487-93.
171. Ananthakrishnan AN, Long MD, Martin CF, Sandler RS, Kappelman MD. Sleep disturbance and risk of active disease in patients with crohn's disease and ulcerative colitis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2013;**11**:965-71.
172. Ali T, Madhoun MF, Orr WC, Rubin DT. Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients. *Inflammatory bowel diseases* 2013;**19**:2440-3.
173. Simian D, Moreno M, Flores L*, et al.* P-071 quality of sleep in chilean ibd patients. *Inflammatory bowel diseases* 2016;**22**:S31-S2.
174. Ali T, Madhoun MF, Crosby A, Orr WC, Rubin DT. Poor sleep quality predicts disease relapse in patients with inflammatory bowel disease. *Gastroenterology* 2013;**144**:S12.

175. Gracie DJ, Irvine AJ, Sood R*, et al.* Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: A systematic review and meta-analysis. *The lancet Gastroenterology & hepatology* 2017;**2**:189-99.
176. McCombie AM, Mulder RT, Gearry RB. Psychotherapy for inflammatory bowel disease: A review and update. *Journal of Crohn's & colitis* 2013;**7**:935-49.
177. Moser G. The role of hypnotherapy for the treatment of inflammatory bowel diseases. *Expert Rev Gastroenterol Hepatol* 2014;**8**:601-6.
178. Langhorst J, Wulfert H, Lauche R*, et al.* Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. *Journal of Crohns & Colitis* 2015;**9**:86-106.
179. Gerbarg PL, Jacob VE, Stevens L*, et al.* The effect of breathing, movement, and meditation on psychological and physical symptoms and inflammatory biomarkers in inflammatory bowel disease: A randomized controlled trial. *Inflammatory bowel diseases* 2015;**21**:2886-96.
180. Neilson K, Ftanou M, Monshat K*, et al.* A controlled study of a group mindfulness intervention for individuals living with inflammatory bowel disease. *Inflammatory bowel diseases* 2016;**22**:694-701.
181. Norton C, Czuber-Dochan W, Artom M, Sweeney L, Hart A. Systematic review: Interventions for abdominal pain management in inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2017;**46**:115-25.
182. Ceballos C, Bao R, Dunkin D*, et al.* Complementary and alternative medicine use at a single pediatric inflammatory bowel disease center. *Gastroenterology nursing : the official journal of the Society of Gastroenterology Nurses and Associates* 2014;**37**:265-71.
183. Cotton S, Humenay Roberts Y, Tsevat J*, et al.* Mind-body complementary alternative medicine use and quality of life in adolescents with inflammatory bowel disease. *Inflammatory bowel diseases* 2010;**16**:501-6.
184. Sharma P, Poojary G, Dwivedi SN, Deepak KK. Effect of yoga-based intervention in patients with inflammatory bowel disease. *Int J Yoga Therap* 2015;**25**:101-12.
185. Cramer H, Schäfer M, Schöls M*, et al.* Randomised clinical trial: Yoga vs written self-care advice for ulcerative colitis. *Alimentary pharmacology & therapeutics* 2017;**45**:1379-89.
186. Ford AC, Quigley EM, Lacy BE*, et al.* Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: Systematic review and meta-analysis. *The American journal of gastroenterology* 2014;**109**:1350-65; quiz 66.
187. Pacific WROftW. Who international standard terminologies on traditional medicine in the western pacific region. 2007.

188. Deng H, Shen X. The mechanism of moxibustion: Ancient theory and modern research. *Evid Based Complement Alternat Med* 2013;**2013**:379291.
189. Lee DH, Kim JI, Lee MS*, et al.* Moxibustion for ulcerative colitis: A systematic review and meta-analysis. *BMC gastroenterology* 2010;**10**:36.
190. Bao C, Liu P, Liu H*, et al.* Different brain responses to electro-acupuncture and moxibustion treatment in patients with crohn's disease. *Sci Rep* 2016;**6**:36636.
191. Bao CH, Zhao JM, Liu HR*, et al.* Randomized controlled trial: Moxibustion and acupuncture for the treatment of crohn's disease. *World journal of gastroenterology* 2014;**20**:11000-11.
192. Joos S, Brinkhaus B, Maluche C*, et al.* Acupuncture and moxibustion in the treatment of active crohn's disease: A randomized controlled study. *Digestion* 2004;**69**:131-9.
193. Ma X. Acupuncture treatment for 76 cases of ulcerative colitis. *Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan* 2005;**25**:264-5.
194. Zhou EH, Liu HR, Wu HG*, et al.* Down-regulation of protein and mrna expression of il-8 and icam-1 in colon tissue of ulcerative colitis patients by partition-herb moxibustion. *Digestive diseases and sciences* 2009;**54**:2198-206.
195. Joos S, Wildau N, Kohnen R*, et al.* Acupuncture and moxibustion in the treatment of ulcerative colitis: A randomized controlled study. *Scandinavian journal of gastroenterology* 2006;**41**:1056-63.
196. Ji J, Lu Y, Liu H*, et al.* Acupuncture and moxibustion for inflammatory bowel diseases: A systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med* 2013;**2013**:158352.
197. Schneider A, Streitberger K, Joos S. Acupuncture treatment in gastrointestinal diseases: A systematic review. *World journal of gastroenterology* 2007;**13**:3417-24.
198. Ernst E. Chiropractic spinal manipulation for back pain. *Br J Sports Med* 2003;**37**:195-6; discussion 6.
199. P610. Osteopathy and improving the quality of life in crohn's disease. *Journal of Crohn's and Colitis* 2015;**9**:S385-S.
200. Bernstein CN. Treatment of ibd: Where we are and where we are going. *The American journal of gastroenterology* 2015;**110**:114-26.
201. Rawsthorne P, Shanahan F, Cronin NC*, et al.* An international survey of the use and attitudes regarding alternative medicine by patients with inflammatory bowel disease. *The American journal of gastroenterology* 1999;**94**:1298-303.

202. Oxelmark L, Lindberg A, Lofberg R*, et al.* Use of complementary and alternative medicine in swedish patients with inflammatory bowel disease: A controlled study. *European journal of gastroenterology & hepatology* 2016;**28**:1320-8.
203. Piche T, Pishvaie D, Tirouvaziam D*, et al.* Osteopathy decreases the severity of ibs-like symptoms associated with crohn's disease in patients in remission. *European journal of gastroenterology & hepatology* 2014;**26**:1392-8.
204. Singh S, Dulai PS, Zarrinpar A, Ramamoorthy S, Sandborn WJ. Obesity in ibd: Epidemiology, pathogenesis, disease course and treatment outcomes. *Nat Rev Gastroenterol Hepatol* 2017;**14**:110-21.
205. Gleeson M, Bishop NC, Stensel DJ*, et al.* The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol* 2011;**11**:607-15.
206. Bernstein CN, Kraut A, Blanchard JF*, et al.* The relationship between inflammatory bowel disease and socioeconomic variables. *The American journal of gastroenterology* 2001;**96**:2117-25.
207. Khalili H, Ananthakrishnan AN, Konijeti GG*, et al.* Physical activity and risk of inflammatory bowel disease: Prospective study from the nurses' health study cohorts. *BMJ* 2013;**347**:f6633.
208. Persson PG, Leijonmarck CE, Bernell O, Hellers G, Ahlbom A. Risk indicators for inflammatory bowel disease. *Int J Epidemiol* 1993;**22**:268-72.
209. Wang Q, Xu KQ, Qin XR*, et al.* Association between physical activity and inflammatory bowel disease risk: A meta-analysis. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2016;**48**:1425-31.
210. Pérez CA. Prescription of physical exercise in crohn's disease. *Journal of Crohn's & colitis* 2009;**3**:225-31.
211. Robinson RJ, Krzywicki T, Almond L*, et al.* Effect of a low-impact exercise program on bone mineral density in crohn's disease: A randomized controlled trial. *Gastroenterology* 1998;**115**:36-41.
212. Loudon CP, Corroll V, Butcher J, Rawsthorne P, Bernstein CN. The effects of physical exercise on patients with crohn's disease. *The American journal of gastroenterology* 1999;**94**:697-703.
213. Elsenbruch S, Langhorst J, Popkirowa K*, et al.* Effects of mind-body therapy on quality of life and neuroendocrine and cellular immune functions in patients with ulcerative colitis. *Psychother Psychosom* 2005;**74**:277-87.
214. Ng V, Millard W, Lebrun C, Howard J. Low-intensity exercise improves quality of life in patients with crohn's disease. *Clin J Sport Med* 2007;**17**:384-8.

215. Klare P, Nigg J, Nold J*, et al.* The impact of a ten-week physical exercise program on health-related quality of life in patients with inflammatory bowel disease: A prospective randomized controlled trial. *Digestion* 2015;**91**:239-47.
216. Jones PD, Kappelman MD, Martin CF*, et al.* Exercise decreases risk of future active disease in patients with inflammatory bowel disease in remission. *Inflammatory bowel diseases* 2015;**21**:1063-71.
217. Peters HP, De Vries WR, Vanberge-Henegouwen GP, Akkermans LM. Potential benefits and hazards of physical activity and exercise on the gastrointestinal tract. *Gut* 2001;**48**:435-9.
218. Tew GA, Carpenter R, Seed M*, et al.* Feasibility of high-intensity interval training and moderate-intensity continuous training in adults with inactive or mildly active crohn's disease: Study protocol for a randomised controlled trial. *Pilot Feasibility Stud* 2017;**3**:17.
219. Monroe CM. Valuable steps ahead: Promoting physical activity with wearables and incentives. *Lancet Diabetes Endocrinol* 2016;**4**:960-1.